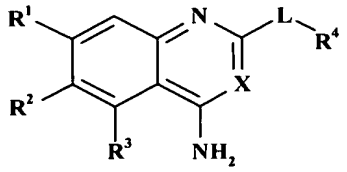
PROCESS FOR THE PRODUCTION OF QUINAZOLINES

This application claims priority to U.S. Serial No. 10/144,337, filed May 13, 2002, now allowed, which claims priority to U.S. Provisional No. 60/301,750, filed June 28, 2001, which claims priority to British Application Serial No. 0112061.7, filed May 18, 2001.

The present invention relates to a novel process for producing quinazoline compounds which are useful in therapy. More specifically, the compounds are useful in the treatment of benign prostatic hyperplasia.

International Patent Application WO 98/30560 discloses a number of substituted quinoline and quinazoline compounds of formula (I) which find use in the treatment of benign prostatic hyperplasia;



I

wherein

R^1 represents C_{1-4} alkoxy optionally substituted by one or more fluorine atoms;

R^2 represents H or C_{1-6} alkoxy optionally substituted by one or more fluorine atoms;

R^3 represents a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring being optionally substituted by one or more groups selected from halogen, C_{1-4} alkoxy, C_{1-4} alkyl and CF_3;

R^4 represents a 4-, 5-, 6-, or 7-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring being optionally fused to a benzene ring or a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring system as a whole being optionally substituted by one or more groups independently selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, $CONR^8R^9$, $SO_2NR^8R^9$, $(CH_2)_bNR^8R^9$ and $NHSO_2(C_{1-4}$ alkyl), and when S is a member of the ring system, it may be substituted by one or two oxygen atoms;

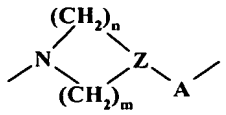
R^8 and R^9 independently represent H or C_{1-4} alkyl, or together with the N atom to which they are attached they may represent a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S;

b represents 0, 1, 2 or 3;

X represents CH or N; and

L is absent,

or represents a cyclic group of formula Ia,



Ia

in which N is attached to the 2-position of the quinoline or quinazoline ring;

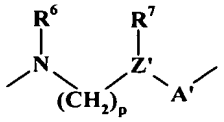
A is absent or represents CO or SO_2;

Z represents CH or N;

m represents 1 or 2, and in addition, when Z represents CH, it may represent 0; and

n represents 1, 2 or 3, provided that the sum of m and n is 2, 3, 4 or 5;

or represents a chain of formula Ib,



Ib

in which N is attached to the 2-position of the quinoline or quinazoline ring;

A' and Z' have the same significance as A and Z above, respectively;

R^6 and R^7 independently represent H or C_{1-4} alkyl; and

p represents 1, 2 or 3, and in addition, when Z' represents CH, it may represent 0.

The compounds of formula (I) in which X = N and L is absent are of particular interest. Of these compounds, 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline is of special interest.

According to WO98/30560, the compounds of formula (I) can be produced by a number of processes. However, none of these processes involves the condensation of the two main parts of the molecule in a convergent synthesis and each process suffers disadvantages.

The routes described in WO 98/30560 suffer the disadvantage that they involve the use of tributyl stannyl pyridine in combination with copper iodide and tetrakis (triphenylphosphine) palladium. One problem of this route is that the tributyl stannyl pyridine is expensive to purchase. The compound is toxic and there are issues of worker safety and concerning the environment. After use, spent reactants are difficult and expensive to dispose of because of the adverse effects organotin compounds have on their surroundings. A further problem with the prior art process is its lack of convergency. A number of synthetic steps are required to produce the quinazoline compounds in the disclosed processes, with each synthetic step leading both to a reduction in yield and increasing the possibility of competing side reactions. Thus the conventional reaction requires effort to purify the product and may not give an optimal yield.

A further problem with the prior art process of WO98/30560 is that large pebble-like aggregates are formed in the reactor during the reaction. The identity of these aggregates is not clear but they are believed to be formed of inorganic material derived from the various inorganic additives used during the reaction such as lithium chloride and copper iodide. In this process, there is the risk that the pebble-like aggregates could crack the reactor causing leakage of the reaction medium and the hazard of fire or poisoning. At the very least there is the problem that the reaction leads to scratching of the interior of the reaction vessel thus causing premature wearing of the vessel, poor heat dissipation in the mixture or blocking.

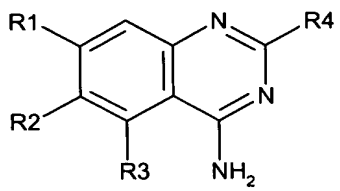
It is an aim of the present invention to provide a synthetically efficient process for the production of quinazoline derivatives which avoids the problems of the prior art process. It is also an aim to provide a process in which the convergency (ie the bringing together of synthetic fragments) is maximised. It is thus an aim to provide a route to the compounds of formula (I) which offers an improved yield relative to the

existing routes. It is a further aim of the process of the present invention to avoid the use of organotin compounds on account of their hazardous nature. It is a further aim of the present invention to provide a process which minimizes the number of

synthetic steps required and which avoids the problem of competing reactions and/or the disposal of hazardous materials.

We have found an improved route to the quinazoline derivatives of formula (I) above.

According to the present invention, there is provided a process for the production of a compound of formula (A) or a pharmaceutically acceptable salt or solvate thereof:



(A)

wherein:

R^1 represents C_{1-4} alkoxy optionally substituted by one or more fluorine atoms;

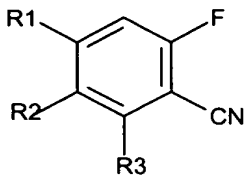
R^2 represents H or C_{1-6} alkoxy optionally substituted by one or more fluorine atoms;

R^3 represents a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring being optionally substituted by one or more groups selected from halogen , C_{1-4} alkoxy, C_{1-4} alkyl and CF_3;

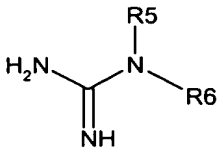
R^4 is a 4-, 5-, 6-, or 7-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring being optionally fused to a benzene ring or a 5- or 6- membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring system as a whole being optionally substituted by one or more groups independently selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, $CONR^7R^8$,

$SO_2NR^7R^8$, $(CH_2)_bNR^7R^8$ and $NHSO_2(C_{1-4}$ alkyl), and when S is a member of the ring system, it may be substituted by 1 or 2 oxygen atoms;

the process comprising condensing a compound of formula (B) with a compound of formula (C):



(B)



(C)

wherein:

R^1 to R^3 are as defined above;

R^5 and R^6 taken together with the N atom to which they are attached represent a 4-, 5-, 6-, or 7-membered N-containing heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring being optionally fused to a benzene ring or a 5- or 6- membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring system as a whole being optionally substituted by one or more groups independently selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, $CONR^7R^8$, $SO_2NR^7R^8$, $(CH_2)_bNR^8R^9$ and $NHSO_2(C_{1-4}$ alkyl), and when S is a member of the ring system, it may be substituted by 1 or 2 oxygen atoms;

R^7 and R^8 independently represent H or C_{1-4} alkyl, or together with the N atom to which they are attached they may represent a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S; and

b represents 0, 1, 2 or 3, and

where necessary or desired, converting the resulting compound of formula (I) into a pharmaceutically acceptable salt or solvate, or converting the resulting salt or solvate into a compound of formula (I).

Preferably R^1 represents methoxy.

Preferably R^2 represents methoxy.

Preferably R^3 represents an aromatic ring. More preferably, R^3 represents pyridinyl, pyrimidinyl, thienyl, furanyl or oxazolyl. Most preferably R^3 represents 2-pyridinyl or 2-pyrimidinyl.

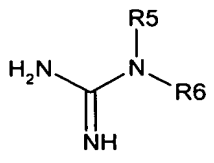
Preferably R^4 represents a saturated 6-membered N-containing ring which is fused to an optionally substituted benzene or pyridine ring. More preferably, R^4 represents a tetrahydroisoquinoline ring system. Most preferably, R^4 is 5-methylsulfonylamino tetrahydroisoquinoline.

Most preferably, the process is used to prepare 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline.

Preferably the reaction is carried out in a polar aprotic solvent. The polar aprotic solvent is preferably dimethylsulfoxide.

Preferably the reaction is carried out in the presence of a base. More preferably, the base is an alkali metal carbonate. Most preferably, the base is caesium carbonate.

In a further aspect of the present invention, there is provided a process wherein the compound of formula (C):



(C)

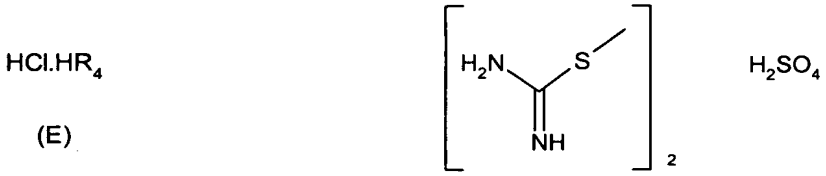
wherein;

R^5 and R^6 taken together represent a 4-, 5-, 6-, or 7-membered N-containing heterocyclic ring optionally containing at least one further heteroatom selected from N, O and S, the ring being optionally fused to a benzene ring or a 5- or 6- membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring system as a whole being optionally substituted by one or more groups independently selected from OH, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, $CONR^7R^8$, $SO_2NR^7R^8$, $(CH_2)_bNR^8R^9$ and $NHSO_2(C_{1-4}$ alkyl), and when S is a member of the ring system, it may be substituted by 1 or 2 oxygen atoms;

R^7 and R^8 independently represent H or C_{1-4}alkyl, or together with the N atom to which they are attached they may represent a 5- or 6-membered heterocyclic ring containing at one heteroatom selected from N, O and S; and

b represents 0, 1, 2 or 3

is formed by reaction of a compound of formula (E) with a compound of formula (F)



(E) (F)

Preferably, R^5 and R^6 together with the N atom to which they are attached represent a saturated 6-membered N-containing ring which is fused to an optionally substituted benzene or pyridine ring.

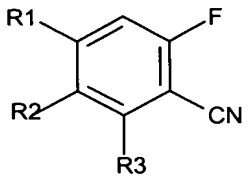
More preferably, R^5 and R^6 together with the N atom to which they are attached represent a tetrahydroisoquinoline ring system.

Most preferably, R^5 and R^6 together with the N atom to which they are attached represent 5-methylsulfonylamino tetrahydroisoquinoline.

Most preferably, the process is used to prepare *N*-(2-amidino-1,2,3,4-tetrahydro-5-isoquinolyl)methanesulfonamide.

Preferably, the reaction is carried out in the presence of an aqueous base. Most preferably, the reaction is carried out in the presence of aqueous sodium hydroxide.

In another aspect of the invention, there is provided a process wherein the compound of formula (B):



(B)

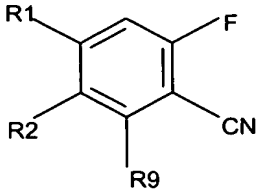
wherein

R^1 represents C_{1-4} alkoxy optionally substituted by one or more fluorine atoms;

R^2 represents H or C_{1-6} alkoxy optionally substituted by one or more fluorine atoms; are as defined above; and

R^3 represents a 5- or 6-membered heterocyclic ring containing at least one heteroatom selected from N, O and S, the ring being optionally substituted by one or more groups selected from halogen , C_{1-4} alkoxy, C_{1-4} alkyl and CF_3;

is formed by reaction of the compound of formula (D):



(D)

wherein R^1 and R^2 are as defined above; and
R^9 is a leaving group;

with a pyridine derivative.

Preferably R^9 is iodine.

Preferably the pyridine derivative is a pyridyl boronate.

Most preferably, the process is used to prepare 6-fluoro-3,4-dimethoxy-2-(2-pyridyl)benzonitrile.

Preferably, the reaction is carried out in a polar aprotic solvent. More preferably, the polar aprotic solvent is dioxane.

Preferably, the reaction is carried out at the reflux temperature of the solvent.

Preferably, the reaction is carried out in the presence of a catalyst. More preferably, the catalyst is a palladium (0) catalyst.

Preferably, the reaction is carried out for a period of from 2 hours to 8 hours. More preferably, the reaction is carried out for a period of from 5 hour to 6 hours.

Preferably, the pyridine derivative is added in a number of discrete aliquots at intervals during the course of the reaction. The pyridyl derivative, preferably pyridyl boronate, may be added in equal or different aliquots. Preferably, the aliquot added at the start of the reaction represents about 20 to 40% of the total amount to be added. More preferably, the intervals between addition of the pyridyl boronate are from 30 minutes to 1 hour and 30 minutes.

The invention is illustrated by the following examples in which the following abbreviations may be used:

DMSO = dimethylsulfoxide

DCM = dichloromethane

THF = tetrahydrofuran

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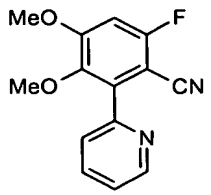
Example 1

6-Fluoro-3,4-dimethoxy-2-(2-pyridyl)benzonitrile



a) Preparation of the pyridyl boronate.

Under nitrogen, to a stirred, cooled (-30°C) solution of 2-bromopyridine (5.0g, 31.6 mmol) and triisopropylborate (5.95g, 31.6 mmol) in anhydrous THF (50ml) was added n-butyllithium (19.8ml of a 1.6M solution in hexanes, 32 mmol) over *ca.* 30 mins keeping the internal temperature in the range -20°C to -15°C. The resulting brown suspension was left to stir for *ca.* 1 hour in the temperature range -20°C to -15°C and then warmed to room temperature over *ca.* 1 hour. The resulting suspension was filtered, the solid collected and dried *in vacuo* overnight at ca. 45°C. The resulting pale brown solid (5.45g) was assumed to be 31.6 mmol of the pyridyl boronate (*i.e.* the procedure had given a 100% yield).

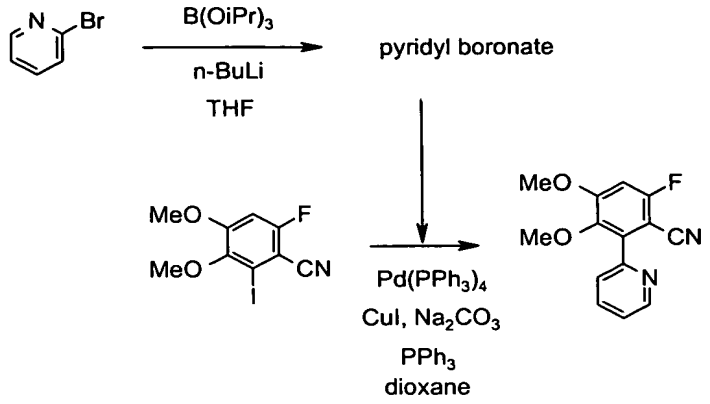
b) Preparation of 6-fluoro-2-iodo-3,4-dimethoxybenzonitrile

The 6-fluoro-2-iodo-3,4-dimethoxybenzonitrile is obtained from the corresponding 6-nitro-2-iodo-3,4-dimethoxybenzonitrile compound (prepared in Example 1d of WO98/30560) by reaction of the latter with an excess of tertbutylammonium fluoride. 6-Nitro-2-iodo-3, 4-dimethoxybenzonitrile (60g) was slurried in dry THF (300ml) at 0°C under an atmosphere of nitrogen. A 5 molar excess of an aqueous solution of tertbutylammonium fluoride was added slowly over a period of 20 minutes to the slurry and the temperature of the mixture was maintained below 5°C. The mixture was stirred at room temperature for a further 18 hours and then cooled to 0°C. Water (600 ml) was added slowly to the mixture which was maintained at a temperature below 5°C, followed by DCM (600ml). The resulting phases were separated and the solvent was removed from the organic phase under reduced

pressure to yield an oily residue. The oily residue was treated with methanol (210ml) and allowed to stand overnight. The resulting solid was recovered from the methanol by filtration and dried to yield 27g of the title compound as a solid. The solid was further purified by treating with methanol and allowing to stand overnight. The solid was recovered by filtration and drying to yield 23.2g (42%) of the title compound having HPLC purity of 92%.

c) Preparation of 6-fluoro-3,4-dimethoxy-2-(2-pyridyl)benzonitrile

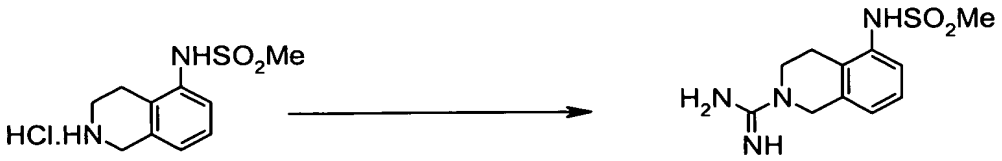
Under nitrogen, stirred dioxane (20 ml) at 80°C was charged with 6-fluoro-2-iodo-3,4-dimethoxybenzonitrile from Example 1b (1.0g, 3.3mmol), tetrakis(triphenylphosphine) palladium-(0) (0.19g, 0.16 mmol), the pyridyl boronate from Example 1a (1.22g, estimated to be 7.1 mmol), copper(I)iodide (0.25g, 1.3 mmol), sodium carbonate (0.69g, 6.5 mmol) and triphenylphosphine (0.17g, 0.65 mmol) and the resulting brown slurry heated to reflux. Further portions of the pyridyl boronate were added at the following times after the reaction had reached reflux; 0.61g after *ca.* 30 mins, 0.61g after *ca.* 1 hour, 0.61g after *ca.* 1 hour 30 mins, 0.61g after *ca.* 2 hours 30 mins, 0.61g after *ca.* 3 hours, 0.30g after *ca.* 4 hours. After a total of *ca.* 5 hours at reflux the reaction was allowed to cool to room temperature, water (10 ml) and ethyl acetate (20 ml) were added and the resulting mixture allowed to stir for *ca.* 15 mins. After this time, the mixture was filtered through Arbocel ™ and the pad washed with ethyl acetate (20 ml). The phases were separated and the aqueous phase extracted with ethyl acetate (20 ml). The organic phases were combined and stripped to a brown oil. Acetonitrile was added, the mixture warmed to reflux and left to cool to room temperature overnight. The resulting suspension was filtered to give a cream solid that was dried *in vacuo* overnight at 45°C to give 0.42g of the product (49%).



Example 2

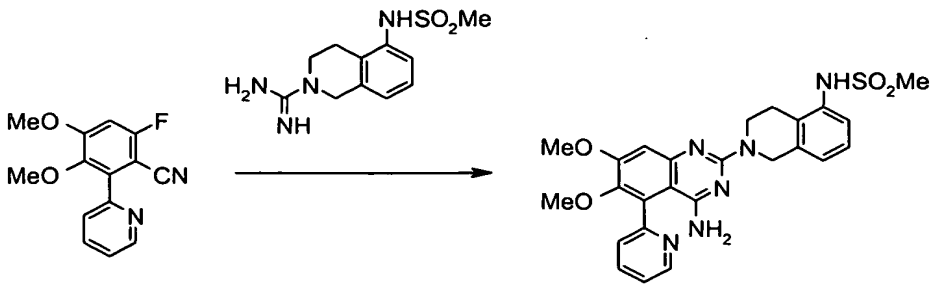
Preparation of *N*-(2-amidino-1,2,3,4-tetrahydro-5-isoquinolyl)methanesulfonamide

To a stirred suspension of *N*-(1,2,3,4-tetrahydro-5-isoquinolyl)methanesulfonamide hydrochloride prepared as described in Example 19b of WO98/30560 (100g, 0.38 mol) and 2-methyl-2-thiopseodourea sulfate (159g, 0.57 mol) in water (1.5l) was added 2N aqueous sodium hydroxide (764ml, 1.53 mol). The resulting solution was warmed to 80°C and stirred at this temperature for *ca.* 6 hours and then left to cool to room temperature overnight. Further 2-methyl-2-thiopseudourea sulfate (27g, 0.10 mol) and 2N aq. sodium hydroxide (48 ml, 0.10 mol) were charged and the mixture heated at 80°C for 1 hour. After this time the resulting suspension was cooled to room temperature, filtered, washed with water (1l) to give a white solid that was dried *in vacuo* overnight at 50°C to give 91.0 g of the product (89%).



Example 3

4-Amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline



To a 3-necked flask equipped with a mechanical stirrer was charged 6-fluoro-3,4-dimethoxy-2-(2-pyridinyl)benzonitrile, (50.0g, 194 mmole), 5-[(methylsulfonyl)amino]-3,4-dihydro-2-isoquinolinecarboximidamide (99.5g, 371 mmole, 1.96equiv),Cs_2CO_3 (150g, 416mmole, 2.37equiv) and *Sureseal* ™ DMSO (150ml, $3mlg^{-1}$). The mixture was slurried at ambient temperature under a N_2 atmosphere. The resultant viscous slurry was heated to 94-97°C for 21hrs then allowed to cool to 40°C. A sample was taken before cooling down for HPLC which indicated 2.4% demethylated impurity, 62% product, 9.6% unreacted starting material. As the percentage of demethylated impurity increases with time, the reaction was deemed complete. Water (500ml) and CH_2Cl_2 (500ml) was added to the reaction and the resultant mixture was stirred for 1hrs at ambient temperature. Arbocel ™ (40g) was added and stirring was continued for 5 min. The Arbocel ™ was filtered off and the filtrate separated into two phases which were separated. The filter pad was collected and re-slurried in DCM 1000ml for 10min and the slurry was filtered. The filtrate from the slurry of DCM and the filter pad was used to extract the aqueous phase. The combined organic extracts was concentrated in *vacuo* to a brown oil (DMSO concentrate of product). EtOH (550ml, $11mlg^{-1}$ w.r.t 6-fluoro-3,4-dimethoxy-2-(2-pyridyl)benzonitrile) was added to the DMSO concentrate and the mixture was heated to reflux and allowed to cool to ambient temperature and a solid precipitated. The solid was collected by filtration and dried in *vacuo* at 50°C overnight to yield 54g of the product, HPLC purity 95%. The product can be further purified by a MeCN re-slurry.